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ORIGINAL ARTICLE

Reproducibility of Musculoskeletal Ultrasound for Determining Monosodium Urate Deposition: Concordance Between Readers

RENNIE G. HOWARD,[1] MICHAEL H. PILLINGER,[1] SOTERIOS GYFTOPOULOS,[1] RALF G. THIELE,[2] CHRISTOPHER J. SWEARINGEN,[3] AND JONATHAN SAMUELS[1]

Objective. **Criteria for sonographic diagnosis of monosodium urate (MSU) crystal deposition have been developed, but the interreader reproducibility of this modality is not well established. We therefore assessed agreement using a systematic approach.**

Methods. **Fifty male subjects ages 55–85 years were recruited during primary care visits to an urban Veterans Affairs hospital, and were assessed by musculoskeletal ultrasound (US) of the knees and first metatarsophalangeal (MTP) joints to evaluate for the double contour sign and tophi as evidence of MSU crystal deposition. Images were read by 2 blinded rheumatologists trained in musculoskeletal US, and the degree of concordance was determined for individual subjects, total joints, femoral articular cartilage (FAC), and first MTP joints. Subjects were further categorized into 3 diagnostic groups: gout, asymptomatic hyperuricemia (no gout, serum uric acid [UA] ≥6.9 mg/dl), and controls (no gout, serum UA ≤6.8 mg/dl), and reader concordance within these 3 groups was assessed.**

Results. **We observed almost perfect agreement between readers for 1) individual subjects (yes/no; n = 50, 100% agreement, $\kappa = 1.000$), 2) total joints (n = 200, 99% agreement, $\kappa = 0.942$), 3) FAC (n = 100, 99% agreement, $\kappa = 0.942$), and 4) first MTP joints (n = 100, 99% agreement, $\kappa = 0.942$). Furthermore, findings by side (right/left) and diagnostic group (gout, asymptomatic hyperuricemia, control) showed substantial to almost perfect concordance for all measures. MSU deposition was seen most commonly in gout patients, and deposition was also seen in some subjects with asymptomatic hyperuricemia, but in only 1 control.**

Conclusion. **Musculoskeletal US is reliable for detecting MSU deposition in FAC and first MTP joints in gout and asymptomatic hyperuricemia.**

INTRODUCTION

The role of musculoskeletal ultrasound (US) in studying monosodium urate (MSU) deposition is rapidly evolving. As a relatively inexpensive imaging approach that does not involve exposure to radiation, musculoskeletal US permits both dynamic assessment of joints and identification of inflammation using power Doppler technology to show microvascular blood flow. In gout, musculoskeletal US has been shown to detect various findings, from free-floating MSU crystals in the synovial fluid ("snowstorm appearance") (1), to MSU crystal deposition on the superficial margin of the articular cartilage ("double contour" sign), to the presence of clinical and subclinical tophaceous deposits and erosions (2). Using power Doppler, one study showed evidence of persistent mild inflammation in patients with asymptomatic chronic tophaceous gout (3).

As compared to radiograph, musculoskeletal US may detect findings in gout at an earlier stage, and with more

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[1]Rennie G. Howard, MD, Michael H. Pillinger, MD, Soterios Gyftopoulos, MD, Jonathan Samuels, MD: New York University Langone Medical Center, New York University Hospital for Joint Diseases, and New York Harbor VA Health Care System New York Campus, New York; [2]Ralf G. Thiele, MD: University of Rochester, Rochester, New York; [3]Christopher J. Swearingen, PhD: University of Arkansas for Medical Sciences, Little Rock.

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Address correspondence to Rennie G. Howard, MD, New York University Hospital for Joint Diseases, 301 East 17th Street, Room 1410, New York, NY 10003. E-mail: rennie.howard@nyumc.org.

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Significance & Innovations

- Blinded rheumatologists with expertise in musculoskeletal ultrasound (US) had substantial to almost perfect correlation in their recognition of monosodium urate (MSU) deposition on cartilage of the femoral articular surfaces and first metatarsophalangeal joints.
- Although MSU deposition was seen most commonly in gout patients, deposition was also seen in some subjects with asymptomatic hyperuricemia, but in only one control. In the setting of lower prevalence of MSU deposition, there was still excellent reproducibility between the 2 readers.
- These findings suggest that musculoskeletal US is a reproducible modality for detection of MSU crystal deposition in patients with gout, and suggest that musculoskeletal US may be used to examine patients with asymptomatic hyperuricemia for subclinical deposition of MSU crystals.
- In both gout patients and those with asymptomatic hyperuricemia, musculoskeletal US evidence of MSU deposition may have implications for treatment choices for these patients.

sensitivity for detecting small (<2 mm) erosions (4). Musculoskeletal US and magnetic resonance imaging (MRI) have been reported to be comparable for the detection of tophi (5), although MRI may be superior in its sensitivity to detect erosions (6). Musculoskeletal US also appears to be better than clinical assessment at detecting effusions and synovitis in patients with a history of gout and/or pseudogout (7). Sensitive and specific determination of MSU deposition in and around the joints by musculoskeletal US would have implications for uric acid (UA) management in patients with gout, including indications for starting treatment and the ability to monitor therapeutic responses by following reduction in extent of MSU deposits. In one recent study, sonographic evidence of the "double contour" sign disappeared in gout patients whose serum UA levels were lowered to ≤6 mg/dl for 7 months or more, but not in patients whose levels remained above 6 mg/dl (8). There is also a potential role for musculoskeletal US in patients with high serum UA but no clinical history of gout, a condition otherwise known as asymptomatic hyperuricemia (AH). Two studies found sonographic evidence of MSU deposition in patients with AH (9,10). Whether such patients warrant treatment is yet to be determined. Given that expert consensus has generally favored urate-lowering therapy (ULT) for visible tophi, and both visible and musculoskeletal US–detected tophi may show evidence of accompanying bony erosion, the treatment of musculoskeletal US–detected lesions will deserve serious consideration (11).

With the growing interest in using musculoskeletal US in the setting of gout and AH, there is a need for more studies to confirm the reproducibility of readings. We therefore undertook a study using musculoskeletal US to examine the knee and first metatarsophalangeal (MTP) joints for evidence of MSU deposition. The objectives of this study were to evaluate interreader agreement of positive and negative findings in these joints, and to compare musculoskeletal US findings and interreader concordance in patients with different likelihoods of having MSU deposition, i.e., gout versus patients with AH versus controls.

SUBJECTS AND METHODS

Enrollment and assessment. Male patients were consecutively recruited during routine primary care visits to the New York Harbor Health Care System, New York Campus of the Department of Veterans Affairs. Prior to each primary care clinic session, the electronic medical records of patients scheduled to attend that session were prescreened to identify individuals potentially meeting enrollment requirements. Patients were considered for inclusion if they were male and between ages 55 and 85 years, and were excluded if they had a current or prior history of inflammatory arthritis other than gout (including but not limited to rheumatoid arthritis, psoriatic arthritis, pseudogout, reactive arthritis, Lyme arthritis, and ankylosing spondylitis), asymptomatic chondrocalcinosis of the knee, inflammatory bowel disease, psoriasis, hemochromatosis, hemodialysis, total knee replacement, or history of severe trauma to the knee. Potentially eligible individuals who expressed a willingness to participate were interviewed, immediately after their primary care visit, by our lead investigator (RGH). Eligibility was confirmed and consent was obtained. All subjects were asked to complete a questionnaire on demographics (age and race) and medication use (ULT, colchicine, and diuretics). Subjects also underwent gout assessment using American College of Rheumatology (ACR) clinical criteria (12), and serum UA level was assessed for all subjects (visit 1). Subjects were categorized as belonging to 1 of 3 diagnostic groups: 1) gout (those meeting ACR clinical criteria), 2) AH (no gout per ACR clinical criteria, UA level ≥6.9 mg/dl), and 3) controls (no gout, UA level ≤6.8 mg/dl).

All enrollees subsequently (visit 2) underwent a structured musculoskeletal US evaluation of the bilateral knee (transverse suprapatellar view of the femoral articular cartilage [FAC] in maximal flexion) and first MTP (longitudinal dorsal and medial views) joints to evaluate for "double contour" sign (Figure 1A) and tophi (Figure 1B). These views were chosen as per guidelines for musculoskeletal US in rheumatology (13). "Double contour" was defined as a hyperechoic band over the FAC or metatarsal head cartilage, whereas tophi were identified as hypoechoic to hyperechoic inhomogeneous material often surrounded by a small anechoic rim (14).

Musculoskeletal US was performed by a rheumatologist (RGH) trained in US using a MyLab25 machine (Biosound Esaote), with a frequency of 12 MHz for the knees and 18 MHz for the MTP joints. All musculoskeletal US images were subsequently read by 2 rheumatologists trained in

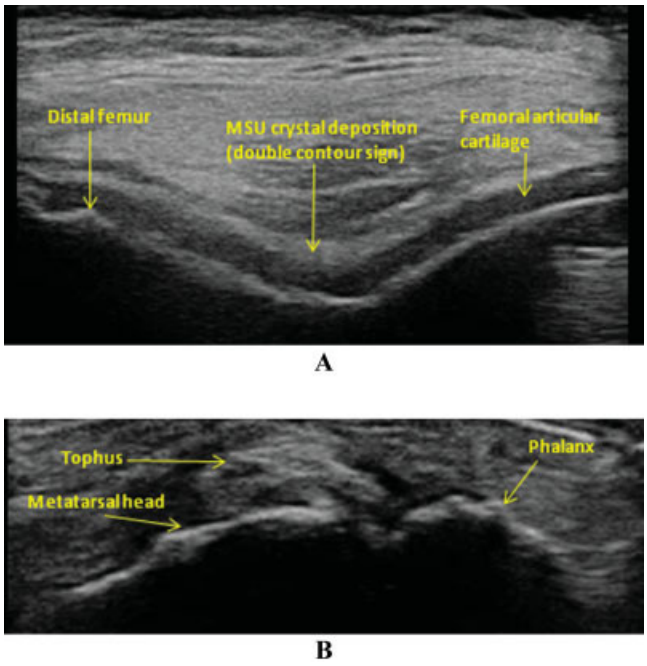

Figure 1. Ultrasound images from 2 study subjects with a history of gout. **A**, "Double contour" sign representing monosodium urate (MSU) deposition on the surface of the femoral hyaline cartilage in one of our study subjects who had a history of gout attacks of the knee. **B**, Gouty tophus at the first metatarsophalangeal joint of one of our study subjects who had a history of repeated gout attacks at this site.

musculoskeletal US interpretation (RGH, JS) who were blinded to subject identity/categories.

US agreement analysis. Agreement between the 2 musculoskeletal US readers was estimated using the kappa statistic and 95% confidence interval (95% CI) (15). Kappa provides a measure of agreement or disagreement beyond what is expected by chance alone. Inference of the kappa statistic is based upon accepted "benchmarks" (16), where $\kappa > 0.80$ = "almost perfect" agreement beyond chance, $0.60 < \kappa \leq 0.80$ = "substantial" agreement, $0.40 < \kappa \leq 0.60$ = "moderate" agreement, $0.20 < \kappa \leq 0.40$ = "fair" agreement, $0.00 < \kappa \leq 0.20$ = "slight" agreement, and $\kappa \leq 0.00$ = "poor" agreement beyond chance. Agreement between the 2 rheumatologists' readings was also estimated for each joint group by side-of-the-body involvement (right/left). The total number of joints assessed in each group, the number of joints affected, and the percentage of observations in agreement were reported along with the kappa statistic. All analysis was completed using Stata, version 11.1.

To determine musculoskeletal US performance in settings of high versus intermediate or low likelihood of MSU deposits, findings were also assessed according to the diagnostic group (gout, AH, control). Differences between musculoskeletal US findings across the 3 subject groups were examined using the expert readings, defined as the readings obtained by the more experienced of the 2 readers (JS); Fisher's exact test was used to evaluate these cross-tabulations with statistical significance set at the level of P values equal to 0.05. To assess whether subjects with positive musculoskeletal US findings corresponded with the presence of a higher number of ACR clinical criteria, we compared the number of clinical criteria present (range 0–8) with the presence of MSU deposition. For this tabulation, we excluded 1 subject with discordant musculoskeletal US findings per the readers. We also compared serum UA levels with the presence of MSU deposition to see if higher values correlated with more frequent MSU deposition.

These studies were approved by the Institutional Review Boards of the New York University School of Medicine and the New York Harbor Healthcare System of the Department of Veterans Affairs.

RESULTS

Fifty subjects were enrolled (Table 1). The mean age of all subjects was 69 years; 38% were white, 40% were African American, 20% were Hispanic, and 2% were "other" (i.e., a single individual of mixed Irish/African descent). The mean serum UA level was 7.1 mg/dl for the group as a whole. Within the subject population as a whole, we observed almost perfect agreement between readers for all defined measures, including the presence (yes/no) of any MSU crystal deposition (as defined by either visible tophus or "double contour" sign, or both) for a given subject (n = 50, 100% agreement; $\kappa = 1.000$, 95% CI 1.000–1.000), total FAC scores, and total first MTP joint scores (Table 2). When findings were further analyzed by side (right/left), concordance was still almost perfect for the right FAC (n = 50, 100% agreement; $\kappa = 1.000$, 95% CI 1.000–1.000), the right first MTP joint (n = 50, 100% agreement; $\kappa = 1.000$, 95% CI 1.000–1.000), and the left first MTP joint (n = 50, 98% agreement; $\kappa = 0.878$, 95% CI 0.643–1.000), and substantial for the left FAC (n = 50, 98% agreement; $\kappa = 0.790$, 95% CI 0.391–1.000). Overall, ratings on only 2 of 200 joints were in disagreement.

Evidence of MSU deposition was found in the same 13 subjects by both observers. These findings were further analyzed by site, with MSU deposition identified in a total of 18 common joints by both readers, and in 1 additional joint by each reader. The latter discrepancy occurred in a single subject with AH, in whom 1 reader found evidence of MSU deposition ("double contour" sign) in the left knee, whereas the other identified an MSU deposit (tophus) in the left first MTP joint. Although both types of MSU deposition were assessed at both the FAC and first MTP joints in all subjects, the "double contour" sign was found only at the FAC, and tophi only at the first MTP joints.

Among the 50 subjects enrolled, 14 (28%) were found to have gout, 17 (34%) were found to have AH, and 19 (38%) were found to have neither (controls). These data are consistent with recent epidemiologic studies suggesting that gout prevalence among all populations, but particularly among older and male patients, has been rising dramatically over the past 4 decades (17). Our gout patients tended to be older and to have more hypertension and renal insufficiency than the AH and control subjects. As summarized in Table 3, we found a high percentage of agreement

Table 1. Patient characteristics*

	All subjects (n = 50)	Gout (n = 14)	Asymptomatic hyperuricemia (n = 17)	Control (n = 19)
Age, mean (range) years	69 (55–85)	73 (61–83)	66 (55–85)	69 (61–84)
Race, no. (%)				
White	19 (38)	4 (29)	7 (41)	8 (42)
African American	20 (40)	9 (64)	6 (35)	5 (26)
Hispanic	10 (20)	1 (7)	3 (18)	6 (32)
Asian	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (2)	0 (0)	1 (6)	0 (0)
Serum uric acid level, mean (range) mg/dl	7.1 (2.9–11.1)	8.1 (2.9–11.1)	8.0 (6.9–10.5)	5.5 (4.4–6.7)
Estimated GFR, mean (range) ml/minute	72 (39–140)	60 (39–97)	73 (51–108)	79 (46–140)
BMI, mean (range) kg/m^2	29.5 (19.6–44.5)	31.1 (26.9–38.3)	30.4 (19.6–44.5)	27.5 (21.0–33.6)
Hypertension, no. (%)	39 (78)	12 (86)	14 (82)	13 (68)
CVD, no. (%)	18 (36)	6 (43)	7 (41)	5 (26)
Diabetes mellitus, no. (%)	24 (48)	5 (36)	9 (53)	10 (53)
Diuretic use, no. (%)	22 (44)	7 (50)	9 (53)	6 (32)
Colchicine, no. (%)		4 (29)		
ULT, no. (%)		6 (43)		
Years since diagnosis of gout, median (range)		10 (2–40)		
Total no. of gout attacks, median (range)		24 (1–132)		

* GFR = glomerular filtration rate; BMI = body mass index; CVD = cardiovascular disease; ULT = urate-lowering therapy.

between readers when analyzing within each diagnostic subject group. We observed almost perfect agreement per kappa scores within each group (gout, AH, controls) for total joints and FAC involvement, almost perfect agreement for first MTP joint involvement in both the gout and control groups, and substantial agreement for the first MTP joints in the AH group. MSU deposition was present on the FAC of the knees or the first MTP joints in 7 (50%) of 14 gout subjects, 5 (29%) of 17 subjects with AH, and 1 (5%) of 19 controls (Fisher's exact test $P = 0.012$). Among the 14 subjects with gout, 10 (36%) of 28 knees had previously been affected by attacks, and we identified the "double contour" sign in 3 (30%) of these 10. Among the remaining 18 knees in the gout population, only 2 (11%) demonstrated the "double contour" sign. Therefore, knees that had previously experienced acute gouty attacks may be more likely to demonstrate MSU crystals on musculoskeletal US than clinically unaffected knees in the same patients, although our sample size was too small to demonstrate a statistically significant difference (odds ratio 3.43, 95% CI 0.30−47.45; Fisher's exact test $P = 0.315$). In the first MTP joints of the 14 gout patients, there was neither an apparent nor a significant difference in MSU deposition between those joints that had versus had not previously experienced an acute attack (Fisher's exact test $P = 0.999$). Seventeen (61%) of 28 first MTP joints had been affected by attacks, and we identified tophi in 4 (24%) of those. Among the 11 clinically unaffected first MTP joints, 3 (27%) showed sonographic evidence of tophi.

When comparing MSU deposition on musculoskeletal US to the number of ACR clinical gout criteria (Table 4), we found that the gout patients in our study met either 6 or 7 (of a possible 8 overall) criteria, and that gout patients in each of these 2 groups had similar rates of MSU deposition. Subjects with AH and controls all reported 0, 1, or 2 criteria, and most subjects with AH and MSU deposition met 0 criteria. Within the control/AH subject groups, there was no increase in MSU deposition with an increasing number of criteria present. Therefore, beyond defining gout, the number of ACR criteria present did not appear to

Table 2. Kappa statistics and percent agreement of 2 independent blinded readers for monosodium urate findings on musculoskeletal ultrasound of 200 joints*

	No. of joints assessed	No. of joints		Agreement, %	κ (95% CI)
		Rater 1	Rater 2		
FAC	100	10	9	99.0	0.942 (0.829–1.000)
First MTP joint	100	9	10	99.0	0.942 (0.829–1.000)
Total joints	200	19	19	99.0	0.942 (0.862–1.000)

* 95% CI = 95% confidence interval; FAC = femoral articular cartilage; MTP = metatarsophalangeal.

Table 3. Kappa statistics and percent agreement of 2 independent blinded readers for monosodium urate findings on musculoskeletal ultrasound per disease group*

	No. of joints assessed	No. of joints affected		Agreement, %	κ (95% CI)
		Rater 1	Rater 2		
FAC					
Gout	28	5	5	100.0	1.000 (1.000–1.000)
AH	34	4	3	97.1	0.841 (0.538–1.000)
Control	38	1	1	100.0	1.000 (1.000–1.000)
Total	100	10	9	99.0	0.942 (0.829–1.000)
First MTP joint					
Gout	28	7	7	100.0	1.000 (1.000–1.000)
AH	34	2	3	97.1	0.785 (0.379–1.000)
Control	38	0	0	100.0	–
Total	100	9	10	99.0	0.942 (0.829–1.000)
Total joints					
Gout	56	12	12	100.0	1.000 (1.000–1.000)
AH	68	6	6	97.1	0.871 (0.571–1.000)
Control	76	1	1	100.0	1.000 (1.000–1.000)
Total	200	19	19	99.0	0.942 (0.862–1.000)

* 95% CI = 95% confidence interval; FAC = femoral articular cartilage; AH = asymptomatic hyperuricemia; MTP = metatarsophalangeal.

be associated with the probability of finding MSU deposition on musculoskeletal US.

Mean serum UA levels were similar in the gout and AH groups, but were lower in controls (Table 1). For patients with gout, mean UA values were 9.4 mg/dl for subjects with MSU crystal deposition (n = 7) versus 6.9 mg/dl for those without (n = 7). For subjects with AH, the mean serum UA level was 8.0 mg/dl for subjects with MSU deposition (n = 5) versus 8.1 mg/dl for those without (n = 12). We further analyzed subjects in the AH group according to serum UA level quartiles; subjects in the lowest quartile had rates of MSU deposition that were similar to those seen in subjects in the highest quartile. Therefore, serum UA levels within the gout group, but not within the AH group (beyond the presence of hyperuricemia per se), appeared to define risk for MSU deposition. Within the gout group, we compared subjects taking ULT (8 of 14) with those who were not (5 of 8), and found that there was less MSU crystal deposition in subjects taking ULT (33%, mean UA level 6.5 mg/dl) versus those who were not (63%, mean UA level 9.4 mg/dl). These data suggest that lowering serum UA to levels below the solubility point (≤6.8 mg/dl) may reduce the likelihood for MSU crystal deposition. In our study, no patients with AH were taking ULT; whether the use of ULT would have reduced the risk of MSU deposition in those patients can therefore not be determined, but would seem plausible based on our data from the gout group. Although patients with a prior history of pseudogout and/or chondrocalcinosis were excluded from enrollment, both readers incidentally observed the presence of chondrocalcinosis in the FAC of a single common patient.

DISCUSSION

Musculoskeletal US has significant potential utility for the diagnosis, severity assessment, decision to treat, and treatment efficacy assessment of patients with gout, but its reproducibility in assessing gouty arthropathy has not been extensively examined. Accordingly, we sought to determine the reproducibility of musculoskeletal US as-

Table 4. Musculoskeletal US findings per number of gout clinical criteria*

No. of clinical gout criteria†	Patients with MSU crystals present on musculoskeletal US	Patients without MSU crystals present on musculoskeletal US	Positive, %
0	4	22	8
1	0	6	0
2	1	2	2
3	0	0	0
4	0	0	0
5	0	0	0
6	4	4	8
7	3	3	6
8	0	0	0

* US = ultrasound; MSU = monosodium urate.
† American College of Rheumatology criteria, ≥6 for diagnosis of gout.

sessments of MSU deposition in a mixed population of subjects with gout, AH, or neither. Our data indicate that musculoskeletal US is a reliable method for detecting UA deposition in both symptomatic and asymptomatic patients, and that its use may add considerably to the management of gout.

We observed significant concordance between our 2 readers in assessing MSU crystal deposition. Specifically, percent agreement was high, and agreement per the kappa statistics was almost perfect for all measures other than the total left FAC and first MTP joints in the AH group, both of which nonetheless also showed substantial agreement. In a pilot analysis conducted before one of our readers had acquired full experience in interpreting images, the kappa values were good but lower than in our actual study (data not shown). In that pilot, the readers were asked to rate their confidence in their readings, and the reported levels of confidence in reading the images of discrepant joints was less than for the concordant ones. Ultrasonographers should therefore be fully trained before applying the technique to clinical use, and may want to consider providing a confidence rating for their readings, particularly when they are uncertain or the quality of the image is suboptimal.

As expected, the majority of musculoskeletal US findings were found in subjects who had a history of gout. In 2 previous studies, the prevalence of the "double contour" sign in knees of gout patients was approximately 40% (7,18), which is somewhat higher than the prevalence observed in our study (25%). These same studies reported the presence of the "double contour" sign in some clinically unaffected knees of gout patients, but the number of such knees was not explicitly reported. In contrast, we report that the frequency of the "double contour" sign in the knee was higher in clinically affected versus unaffected knees of gout patients, although the difference did not achieve statistical significance. The presence of tophi on musculoskeletal US at the first MTP joint in gout patients has been reported in one study at 35% (19), again higher than our findings of approximately 18%. Differences between our study and the prior studies may relate to the fact that we performed fewer views of each joint, limiting our examinations to several highly standardized views. Our study also did not include joints that were currently symptomatic. (In a study in which joints were only examined when symptomatic, 92% of all joints revealed a double contour sign [20].) Based on our data, differences in serum urate levels, disease duration, and ULT do not appear to explain the prevalence differences between previous studies and our own.

In our study, a fairly high percentage of AH subjects demonstrated sonographic evidence of MSU deposition. Prior data on MSU deposition in subjects with AH are limited, but in the one study previously published, 12 (34%) of 35 subjects with AH had tophaceous deposits, with 10 of these subjects having deposition at/around the knee (deposition on the FAC and MTP joints was not reported) (9). Our data show a comparable percentage of affected joints in AH, which was intermediate in prevalence between the gout and control groups. Additional studies will be needed to more definitively establish the prevalence of MSU deposition in subjects with AH, and the extent to which MSU deposition correlates with the degree of hyperuricemia.

Although we excluded patients with a known history of pseudogout or chondrocalcinosis, both of our readers did observe calcium pyrophosphate dihydrate (CPPD) deposition in a single subject on musculoskeletal US images of the FAC of the knee. This observation suggests, but is insufficient to demonstrate, good reproducibility when reading US for CPPD. Importantly, CPPD deposition was easily distinguishable from MSU deposition, as MSU deposition occurs on the surface of the hyaline cartilage producing the "double contour" sign, whereas CPPD deposition appears as a central hyperechoic focus within the cartilage (1,2,7). Although nonurate crystalopathies may have important clinical implications when present, for the purposes of this study, the finding of chondrocalcinosis on musculoskeletal US did not confound our findings of MSU deposition.

Our study had several strengths. In particular, the prospective enrollment of patients, including face-to-face interviews with all patients, permitted us to differentiate subjects into gout, AH, and control groups with a high degree of accuracy. Our study also had several limitations. The relatively small sample size limited our ability to perform subanalyses on the data. As a matter of deliberate design, we did not examine joint fluid to confirm the presence of crystals, since our goal was to compare the musculoskeletal US readings of 2 trained observers. Nonetheless, it might have been helpful to compare musculoskeletal US to crystal diagnoses to confirm that the findings of the "double contour" sign and tophi did indeed identify MSU deposits. In prior studies, musculoskeletal US findings of MSU deposition have been confirmed via needle aspiration of tophi (21), and disappearance of the "double contour" sign and tophi has also been observed with proper ULT (8). In addition, we did not prospectively assess C-reactive protein (CRP) values in order to determine whether the presence of crystals might be associated with chronic inflammation. In a retrospective analysis of 17 of our subjects for whom previous CRP values were available, we saw no clear relationship between CRP levels and MSU deposition (data not shown).

Overall, our findings support musculoskeletal US as a reliable modality for detecting MSU deposition on the FAC and in MTP joints in both gout and AH. Our data further suggest that musculoskeletal US identification of MSU deposition is reproducible both in higher- (i.e., gout) and lower-risk (i.e., control) populations. Since MSU deposition in the form of tophi can be considered an indication for ULT, this type of imaging could be performed noninvasively at the bedside or in the clinic to help direct therapy in gout patients at an earlier stage of disease. Moreover, a role for musculoskeletal US in gout diagnosis per se deserves consideration, particularly when joint fluid analysis is not possible, and especially given the fact that the clinical diagnosis of gout may have a high error rate (22). Since tophi may be associated with bony erosion formation (14), the ability of musculoskeletal US to reliably identify MSU in the joints of patients with AH may also have implications for treatment to prevent possible

future erosions. Although our study confirms the reproducibility of musculoskeletal US findings to detect MSU deposition, musculoskeletal US findings have not yet been fully correlated with pathologic examination. If findings in individuals with AH can be confirmed in this manner, these cases may be more appropriately labeled as "subclinical gout" instead of "asymptomatic hyperuricemia."

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Howard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Howard, Pillinger, Thiele, Samuels.
Acquisition of data. Howard, Gyftopoulos, Samuels.
Analysis and interpretation of data. Howard, Pillinger, Thiele, Swearingen, Samuels.

REFERENCES

1. Grassi W, Meenagh G, Pascual E, Filippucci E. "Crystal clear": sonographic assessment of gout and calcium pyrophosphate deposition disease. Semin Arthritis Rheum 2006;36:197–202.
2. Dalbeth N, McQueen FM. Use of imaging to evaluate gout and other crystal deposition disorders. Curr Opin Rheumatol 2009;21:124–31.
3. Thiele RG, Schlesinger N. Ultrasonography shows active inflammation in clinically unaffected joints in chronic tophaceous gout [abstract]. Arthritis Rheum 2009;60 Suppl:S565.
4. Schueller-Weidekamm C, Schueller G, Aringer M. Impact of sonography in gouty arthritis: comparison with conventional radiography, clinical examination, and laboratory findings. Eur J Radiol 2007;62:437–43.
5. Perez-Ruiz F, Martin I, Canteli B. Ultrasonographic measurement of tophi as an outcome measure for chronic gout. J Rheumatol 2007;34:1888–93.
6. Carter JD, Kedar RP, Anderson SR, Osorio AH, Albritton NL, Gnanashanmugam S, et al. An analysis of MRI and ultrasound imaging in patients with gout who have normal plain radiographs. Rheumatology (Oxford) 2009;48:1442–6.
7. Filippucci E, Scire CA, Delle Sedie A, Iagnocco A, Riente L, Meenagh G, et al. Ultrasound imaging for the rheumatologist XXV: sonographic assessment of the knee on patients with gout and calcium pyrophosphate deposition disease. Clin Exp Rheumatol 2010;28:2–5.
8. Thiele RG, Schlesinger N. Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheumatol Int 2010;30:495–503.
9. Puig JG, de Miguel E, Castillo MC, Rocha AL, Martinez MA, Torres RJ. Asymptomatic hyperuricemia: impact of ultrasonography. Nucleosides Nucleotides Nucleic Acids 2008;27:592–5.
10. Pineda C, Amezcua-Guerra LM, Solano C, Rodriguez-Henriquez P, Hernandez-Diaz C, Vargas A, et al. Joint and tendon subclinical involvement suggestive of gouty arthritis in asymptomatic hyperuricemia: an ultrasound controlled study. Arthritis Res Ther 2011;13:R4.
11. Chen LX, Schumacher HR. Gout: can we create an evidence-based systematic approach to diagnosis and management? Best Pract Res Clin Rheumatol 2006;20:673–84.
12. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DL, Yu T. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895–900.
13. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641–9.
14. Schlesinger N, Thiele RG. The pathogenesis of bone erosions in gouty arthritis. Ann Rheum Dis 2010;69:1907–12.
15. Fleiss JL, Levin B, Paik MC. The measurement of interrater agreement. In: Statistical methods for rates and proportions. 3rd ed. New York: John Wiley; 2003. p. 598–605.
16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
17. Choi H. Epidemiology of crystal arthropathy. Rheum Dis Clin North Am 2006;32:255–73.
18. Filippucci E, Riveros MG, Georgescu D, Salaffi F, Grassi W. Hyaline cartilage involvement in patients with gout and calcium pyrophosphate deposition disease: an ultrasound study. Osteoarthritis Cartilage 2009;17:178–81.
19. Wright SA, Filippucci E, McVeigh C, Grey A, McCarron M, Grassi W, et al. High-resolution ultrasonography of the first metatarsal phalangeal joint in gout: a controlled study. Ann Rheum Dis 2007;66:859–64.
20. Thiele RG, Schlesinger N. Diagnosis of gout by ultrasound. Rheumatology (Oxford). 2007;46:1116–21.
21. Nalbant S, Corominas H, Hsu B, Chen LX, Schumacher HR, Kitumnuaypong T. Ultrasonography for assessment of subcutaneous nodules. J Rheumatol 2003;30:1191–5.
22. Zhang W, Doherty M. EULAR evidence based recommendations for gout part I: diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1301–11.